UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,215	07/02/2003	Fatih M. Uckun	12152.70USD1	7725

7590 06/27/2005

Atten: Keith Campbell
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903

EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 06/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,215	UCKUN ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of a solid tumor is acknowledged.

Claims 28-40 remain pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-40 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are three issues. First, enablement is lacking for inducing cytotoxicity in any and all cell types. Second, applicants have not shown that the disclosed cathepsin inhibitors are effective against even one kind of inflammation, to say nothing of all types of inflammation. Third, with respect to claim 36, applicants have provided no explanation as to how a polynucleotide could encode a compound that bears either a benzyloxycarbonyl group or a benzoyloxycarboxamide group.

With regard to the first issue, the reality is that if one observes stimulation of

apoptosis in one cell line (as a consequence of incubation with compound "X") one cannot "predict" what other cell lines will undergo reduced apoptosis in the presence of compound "X". The skilled artisan also cannot predict what other cell types will undergo enhanced apoptosis in the presence of compound "X". For example, Fang X. (*Biochemical Journal* **352 Pt 1** 135-43, 2000) discloses that lysophosphatidic acid inhibits apoptosis in fibroblasts; at the same time, Steiner M. R. (*Annals of the New York Academy of Sciences* **905** 132-41, 2000) discloses that lysophosphatidic acid induces apoptosis in neuronal cells. Thus, if a determination is made that a given compound will inhibit apoptosis of a given cell type, the skilled artisan cannot predict the cell types in which apoptosis will be inhibited, and the cell types in which apoptosis will be induced. This conclusion is reinforced by the findings of Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) who discloses that while dexamethasone induces apoptosis in both CD8+ cells and CD4+ cells, Galectin-9 induces apoptosis in CD8+ cells, but fails to induce apoptosis in CD4+ cells.

And even applicants were to limit claim 28 to induction of cytotoxicity in tumor cells, the list of cell types would be extensive. For example, the following types of cancer would be included: breast cancer, prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin

Lymphoma, melanomas of the skin, cancer of the Kidney and Renal Pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary

carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenströom's macroglobulinemia, and heavy chain disease. The skilled oncologist would not find it likely that one agent could induce cytotoxicity in all of these cancer cell types.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Accordingly, "undue experimentation" would be required to determine which cell types will exhibit increased apoptosis (as a result of contact with CATI-1), which will exhibit reduced apoptosis, and which will be unaffected.

As for inflammatory disorders, any of the following could be encompassed:

> acute respiratory distress syndrome, adult respiratory distress syndrome, AIDS, allergies, Alzheimer's disease, amylotropic lateral sclerosis, angina pectoris, antibiotic toxicity, arrythmias, artherosclerosis, arthritis, asthma, atherosclerosis, autoimmune diseases, benign monoclonal gammopathy, bronchitis, cardiac ischemia, cardiovascular diseases, cataracts, cellular damage caused by ionizing radiation, central artery occlusion, Central nervous system ischemia, cerebral palsy, cerebral vascular diseases, chronic granulomatous disease, chronic inflammation, cirrhosis, colitis, Congestive heart failure, connective tissue disorders, corneal graft rejection, Crohn's disease, cystic fibrosis, degenerative diseases of aging, diabetes, diabetes-associated diseases, diabetic retinopathy, diarrhea, emphysema, endocarditis, endometriosis, eye diseases, gastritis, head injury, hemangiomas, hemophiliac joints, hepatitis C, herbicide poisoning, Huntington's chorea, hypertension, hyperthermia, brain injury, hypertrophy, hypoventilation, hypoxia, immune disorders, inflammatory bowel disease, ischemia reperfusion, ischemic bowel disease, kidney disease, kidney tumors, liver disease, lung tumors, macular degeneration, metabolic diseases, diabetes mellitus, multiple organ dysfunction syndrome, multiple organ failure, multiple sclerosis, Myocardial stunning, neovascular glaucoma, nephritis, neurodegenerative diseases, neurodegenerative diseases, neurological diseases, neurological trauma, obesity, ocular angiogenic diseases, pancreatitis, Parkinson's disease, Perinatal hypoxia-induced ischemia, peripheral vascular disease, Placental ischemia and fetal distress, polyposis, prion disease, psoriasis, pulmonary embolism, renal disease, pyrogenic granulomas, renal disease, reperfusion, respiratory viral infections, retinopathy of prematurity, retrolental fibroplasia, rheumatoid arthritis, rubeosis, scleroderma, seizures, senile dementia, senility, sepsis, shock, tissue damage occurring upon administration of chemotherapeutics, spinal cord injury, spongiosiform encephalomyopathy, systemic inflammatory response syndrome, tissue damage after surgery, toxic reactions, transient ischemic attack, transition metal poisoning, transplantation rejection, trauma, traumatic brain injury, traumatic crush injury, ulcerative colitis, and Wilson's disease

There is no evidence that even one of these can be successfully treated with the disclosed cathepsin inhibitor.

The third issue concerns claim 36. Certainly, there is no polynucleotide

that encodes a Cbz (carboxylbenzyloxy) group. Conceivably, an enzyme or group of enzymes could be fashioned which could synthesize a compound which, upon reaction with a peptide, could introduce a Cbz group onto a peptide. However, even here it seems unlikely that this could be accomplished using only compounds that are endogenous to a mammal. The "state of the art" (both past and present) weighs heavily against applicants in regards to claim 36. And certainly, there is no guidance in the specification as to how one might achieve this. Nevertheless, for purposes of discussion, applicants are invited to speculate on what enzymes might be effective to synthesize a peptide bearing a Cbz group using only compounds that are endogenous to a mammal.

✧

Claims 37-40 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites "inhibiting inflammatory disease states". How does one go about "inhibiting" a state, and how does one know when inhibition has been achieved? (The term "treating" could be used, but the §112, first paragraph

rejection will be maintained in either case).

✦

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 37 and 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Abdel-Meguid (USP 6,274,336).

Abdel-Meguid discloses (col 2, line 32+; col 2, lines 41-42) that cathepsin inhibitors can be used to treat arthritis or osteoarthritis.

Thus, the claims are anticipated.

✦

Claims 37 and 39 are rejected under 35 U.S.C. §102(e) as being anticipated by Kolb (USP 6,130,315).

Kolb discloses (col 9, line 63+) that that cathepsin inhibitors can be used to treat arthritis.

Thus, the claims are anticipated.

✧

Claims 37 and 39-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Buyesse (USP 6,506,733).

Buyesse discloses (col 14, line 23+; col 14, line 32+) that cathepsin inhibitors can be used to treat arthritis or osteoarthritis.

Thus, the claims are anticipated.

✧

The "Krueger" reference was stricken from the IDS because it was not received and was not present in the parent file.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.